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# II. Protagonist's Viewpoint

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During the past 2 decades there has been a progressive revision of the role of digitalis in the management of congestive heart failure. The availability of alternative drugs has reduced the dependence of the clinician on digitalis as the principal approach to management of this disorder and has modified the approach to digitalis therapy in those patients in whom a valid indication for the drug continues to exist.

What is the rationale for the use of digoxin in the management of patients with chronic congestive heart failure? We should acknowledge that digoxin is not necessarily the drug of first choice after diuretics in *all* patients with this

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syndrome. Most therapeutic entities pass from a phase of initial (and often unwarranted) enthusiasm that—with recognition of drug failures and unwanted side effects—is followed by a phase of (often unwarranted) disillusionment and pessimism. After years of use, as subsets of patients are defined and dosing regimens are refined, a balanced consensus emerges regarding the risks and benefits of a specific therapeutic approach in various subsets of patients. After 200 years we are reaching this third phase in the case of the cardiac glycosides. Our challenge, therefore, is to define which *subsets* of patients with chronic congestive heart failure have a favorable balance between risk and benefit when treated with digitalis.

**Risks of digitalis therapy.** Although digitalis may produce cardiac and noncardiac side effects, most of these adverse reactions are reversible and do not alter the long-term morbidity and mortality of patients with congestive heart failure. Among more than 4,300 digitalis-treated patients monitored in Boston area hospitals between 1966 and 1975 (1), adverse reactions attributable to digitalis occurred in 12% of patients, but were believed to have possibly contributed to death in only 2 individuals, both of whom had severe congestive heart failure and chronic obstructive pulmonary disease. Thus, only about 0.05% of patients receiving digoxin were reported to have had a fatal episode of toxicity possibly related to digitalis. It is important to note that this record of safety was compiled before the widespread measurement of serum digoxin levels, before digoxin-specific Fab fragments were available for the treatment of advanced and potentially life-threatening drug toxicity and at the time when it was common clinical practice to increase the dose of digitalis to maximal tolerated doses when signs and symptoms of congestive heart failure persisted. Thus, although digitalis toxicity is not rare (2), fatal outcomes during routine clinical use of the drug appear to be quite uncommon. The possibility that digitalis may increase the risk of death in patients recovering from an acute myocardial infarction has been vigorously debated (3–6); if any added risk from digitalis can be validly identified in these studies, the effect appears to be sufficiently small that a very large prospective randomized study would be required to detect such a modest adverse effect on mortality (6,7).

**Hemodynamic benefits of digitalis therapy.** Does digitalis therapy produce sustained hemodynamic effects in patients with chronic heart failure? Nearly every study that has evaluated this question using precise hemodynamic measurements has concluded that the well established short-term effects of digitalis on cardiac performance persist during long-term treatment with the drug. Arnold et al. (8) evaluated the efficacy of digoxin in nine middle-aged patients with severe congestive heart failure, all of whom had an enlarged left ventricle secondary to either ischemic heart disease or dilated cardiomyopathy. Invasive hemodynamic measurements were initially carried out during stable long-term digoxin therapy and were repeated after the drug was discontinued for 6 weeks. The withdrawal of digitalis was accompanied by hemodynamic deterioration in all nine patients, as reflected by a decrease in left ventricular stroke work index and an increase in pulmonary capillary wedge pressure at rest and during exercise; this deterioration was reversed after reinstitution of digitalis therapy. Symptoms of heart failure worsened after the withdrawal of digitalis in five of the nine patients, most notably in those with the most advanced congestive heart failure. These long-term hemodynamic benefits of digitalis at rest were subsequently confirmed in elderly patients by Ware et al. (9) and during exercise by Murray et al. (10). These beneficial effects of digitalis on cardiac performance do not depend on the specific cause of left ventricular systolic dysfunction, but appear to be similar in patients with ischemic, valvular or idiopathic cardiomyopathic disease (11).

**Clinical benefits of digitalis therapy.** Are these hemodynamic benefits translated into the relief of symptoms and an improvement in exercise tolerance? Unfortunately, most studies that have evaluated the efficacy of digitalis have been seriously flawed and convey little useful information on which clinical decisions can be based. In their review of all 16 studies published between 1960 to 1982 that evaluated the efficacy of digitalis in patients with chronic heart failure and normal sinus rhythm, Mulrow et al. (12) concluded that only two studies were both double-blinded and placebo-controlled and, hence, could provide unbiased information. The other studies failed to define clearly their selection of patients, confirm the diagnosis of heart failure or employ adequate controls.

*In the first placebo-controlled, double-blind trial of digoxin in heart failure*, Dobbs et al. (13), utilizing a crossover design, observed that 16 of 46 patients with stable chronic heart failure exhibited symptomatic deterioration when digoxin was replaced by a placebo. However, of the 46 patients in this study, 10 had cor pulmonale and 13 had atrial arrhythmias; unfortunately, the investigators never made clear how many of the 16 patients who required digitalis had atrial fibrillation on entry into the trial. The study also failed to describe how other therapeutic modalities for heart failure (diuretics, for example) were controlled during the crossover from digoxin to placebo.

*The first rigorous, double-blinded, placebo-controlled, randomized trial of digitalis in ambulatory patients with sinus rhythm was conducted by Lee et al. (14).* For purposes of this crossover study, these investigators developed a heart failure score based on both the signs and the symptoms of heart failure. All patients continued to receive diuretics in doses that were considered optimal by the physician caring for the patient. The principal results of this study are shown in Figure 1, which is redrawn from the original publication. The condition of the majority of the patients who entered this study improved during treatment with digoxin (shown

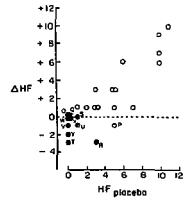


**Figure 1.** Change in heart failure score (ΔHF) when digoxin was substituted for placebo in 25 individual patients with chronic heart failure plotted against the heart failure score of each patient during the placebo phase (HF placebo). Eleven patients, designated by letters O through Y, failed to benefit from digoxin therapy (and are shown on or below the dashed line), whereas the condition of 14 patients improved during the digoxin phase. Of the 11 nonresponders, 10 did not have an audible third heart sound (**closed circles**) during the placebo phase whereas patient P did have an $S_3$ gallop (**open circles**). Seven nonresponders had a heart failure score of zero during the placebo phase, and hence could not have shown improvement; of these, patients O, Q and W had a normal left ventricular ejection fraction (≥0.52) whereas patients X, Y and T had a serum digoxin level of only 0.5 ng/ml. Patients S, U and R also had a normal left ventricular ejection fraction (>0.57). Only patient P with ischemic heart disease failed to show improvement with digoxin despite an adequate serum digoxin level (1.8 ng/ml), a depressed left ventricular ejection fraction (0.13) and a heart failure score of 5 during the placebo phase. Redrawn with permission from Lee et al. (14).

above the dashed zero line). Of the 11 patients whose condition failed to improve, 7 had no symptoms of heart failure (heart failure score = 0) during the placebo phase and, thus, could not (by definition) have shown any improvement during active treatment. Two patients had ischemic heart disease with a normal left ventricular ejection fraction, and four had hypertrophic cardiomyopathy with a left ventricular ejection fraction ≤0.52; these patients with *preserved systolic function would not have been expected to* show improvement with digitalis. Of the 15 patients with systolic left ventricular dysfunction and symptoms of heart failure on placebo, 14 showed a favorable response to long-term treatment with digoxin in the opinion of the blinded observers. Interestingly, each responder (and only one nonresponder) had a third heart sound during placebo therapy, attesting to the presence of severe systolic dysfunction in patients who responded favorably to digitalis. In contrast, in the placebo-controlled study of Fleg et al. (15), in which digitalis was not found to be clinically effective, the majority of enrolled patients were minimally symptomatic and only one patient had a third heart sound.

*The first large scale placebo-controlled clinical trial to evaluate the effects of digitalis on exercise tolerance in patients with heart failure and sinus rhythm was recently completed by DiBianco et al. (16).* This trial was carried out as part of a comparative study of digoxin and milrinone in these same patients. Two hundred thirty patients with continued symptoms of heart failure despite digoxin and diuretics were randomly assigned to continued therapy with digoxin, the withdrawal of digoxin, the addition of milrinone or the substitution of milrinone for digoxin. Most of these patients were in New York Heart Association (NYHA) functional class III. After 3 months of therapy, patients who continued to receive digoxin were better symptomatically and showed a significantly longer exercise tolerance than did patients who had been withdrawn from treatment with the drug. Digoxin also produced a modest but significant increase in left ventricular ejection fraction at rest. No difference in survival was noted between placebo-treated and *digoxin-treated patients in this study over the 3 month period* of observation, but the study was neither large enough nor long enough to have the statistical power needed to allow any definitive statement in this regard.

**Digitalis or vasodilators as first line agents.** Despite numerous studies of the use of vasodilator drugs in patients with chronic heart failure in recent years, we know little about the relative safety and efficacy of these agents when compared with digitalis or about the combined use of digoxin and vasodilators. Some important clues, however, have emerged from a recent report by Gheorghiade et al. (17). These investigators evaluated the effects of intravenous digoxin in 11 patients with severe heart failure whose condition was stabilized with diuretics and vasodilators without treatment with digitalis. The addition of intravenous digoxin increased mean cardiac index by 30%, left ventricular stroke work index by 62% and left ventricular ejection fraction by 38% (from 0.21 to 0.29) and decreased pulmonary capillary wedge pressure by 29%. Five of the 11 patients failed to respond to digoxin, and these patients had nearly normal hemodynamic measurements after optimal therapy with diuretics and vasodilators. In contrast, the six patients who responded dramatically to digoxin had persistent hemodynamic evidence of left ventricular dysfunction despite aggressive therapy with diuretics and vasodilators. These observations are consistent with the view that patients with the most severe left ventricular dysfunction show the most dramatic short-term response to digitalis.

*Only one study has directly compared the long-term clinical effects of digitalis and vasodilators in patients with chronic heart failure.* In this multicenter trial (18), 300 patients treated with diuretics were randomly assigned to therapy with digoxin, captopril or placebo and were followed up for 6 months. The study showed that both digitalis and captopril reduced the need for hospitalizations and emergency room visits for heart failure. Although exercise time and functional class were more favorably affected by captopril than by digoxin, there was no significant difference

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between captopril- and digoxin-treated patients with respect to any symptomatic end point. All of the patients in this study, however, had symptoms of heart failure mild enough to justify the withdrawal of cardiac glycosides; this entry requirement limits the scope of the conclusions that can be drawn from this study. In addition, the power of this study was not sufficiently large to allow any valid inferences to be drawn regarding possible differences in mortality among the three treatment groups.

## Conclusions

Considering the available data as discussed here and elsewhere (19), I would offer the following set of answers to the question "should digoxin be the drug of first choice after diuretics in the treatment of chronic congestive heart failure?"

### *YES, in the Following Subsets*

1. Symptomatic patients with significant left ventricular systolic dysfunction and supraventricular tachyarrhythmias (most often atrial fibrillation) and a rapid ventricular response.
2. Symptomatic patients with substantially impaired left ventricular systolic function at high risk of developing clinically important hypotension on vasodilator therapy.
3. Symptomatic patients with substantially impaired left ventricular systolic function at high risk of developing worsening renal failure on vasodilator therapy.

### *NO, in the Following Subsets*

1. Patients with symptoms of heart failure but with preserved left ventricular systolic function (usually patients with diastolic dysfunction due to cardiac hypertrophy, myocardial ischemia or other causes of reduced ventricular compliance).
2. Patients with mitral stenosis, normal sinus rhythm and no right ventricular failure.
3. Patients with *mild* symptoms of heart failure (NYHA functional class II) who become asymptomatic and have well preserved exercise tolerance while receiving diuretics.

### *UNCERTAIN, in Several Large and Important Subsets of Patients Including*

1. Severely symptomatic patients (NYHA class III or IV) with left ventricular systolic dysfunction of such severity that both digoxin and vasodilators will probably be required (if tolerated) in addition to diuretics. Whereas no reliable data are available that can guide a decision as to whether digoxin or vasodilators should be added first to the diuretic regimen, individual clinical considerations will likely be important; for example, marginal renal function, borderline systemic arterial pressure and marked sinus tachycardia at rest would favor the institution of digoxin therapy before the administration of vasodilators.
2. Patients being treated with diuretics who have sinus rhythm with mild to moderate symptoms due to impaired left ventricular systolic function, preserved renal function and normal or mildly increased systemic arterial pressure. Most of these patients will benefit from digoxin or vasodilators, and it is not clear which therapeutic intervention should be added first. Although both direct-acting vasodilators and converting enzyme inhibitors prolong life in certain patient subsets (20,21), most patients enrolled in the survival trials conducted to date have had severe symptoms and all received background therapy with digitalis.

*It seems clear that the available data allow few sweeping generalizations regarding the relative merits of digoxin and vasodilators in these last two subsets of patients.* The time is long overdue for properly designed and stratified clinical trials to answer important, unresolved questions regarding the effects of digitalis glycosides on the quality of life and the long-term outcome of patients with chronic heart failure.

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# III. Antagonist's Viewpoint

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The role of digitalis in the management of congestive heart failure has been the center of controversy for more than 200 years, but the focus of this debate has changed substantially during the course of clinical investigations with the drug. For a long time, the efficacy of digitalis in the treatment of congestive heart failure in patients with normal sinus rhythm was in doubt. We now know that digitalis can be effective in some patients with chronic heart failure in the absence of atrial fibrillation. For a long time, the safety of digitalis was a source of concern. We now know that digitalis toxicity can be avoided in most patients with chronic heart failure and is not an important drawback to the use of this agent. These issues are no longer sources of controversy; in fact, there is little doubt that digitalis should be used in the treatment of chronic heart failure. We do not know, however, *when* therapy with digitalis should be utilized. This new controversy will likely continue for many years, as new pharmacologic interventions are developed and become accepted as effective therapeutic modalities and thus challenge the choice of digitalis as a first line agent after diuretics in the treatment of patients with symptomatic left ventricular dysfunction.

*How should we decide whether digitalis or a new therapeutic approach (such as vasodilator therapy) should be used after diuretics in chronic heart failure?* We need to compare the effects of these two pharmacologic strategies on the three primary goals of treatment of these severely ill patients: relief of symptoms of heart failure, increase in exercise tolerance and prolongation of life. It is important to note that an increase in cardiac output or in left ventricular ejection fraction should not be considered to be one of the major goals of therapy in patients with symptomatic left ventricular dysfunction because changes in these variables do not parallel changes in symptoms or exercise capacity (1). Which of the treatment options now available (digitalis or vasodilator drugs) provides the most consistent benefits on symptoms and survival in patients with chronic heart failure?

**Effects of digitalis and vasodilators on symptoms.** Although digitalis can improve left ventricular performance in many patients with chronic heart failure, the results of double-blind, placebo-controlled studies have raised concerns that these hemodynamic effects may not be consistently translated into clinical benefits. Fleg et al. (2) noted that the withdrawal of digitalis from patients with chronic heart failure and normal sinus rhythm was accompanied by a small but significant increase in left ventricular end-diastolic dimension and circumferential shortening, but these adverse hemodynamic changes were not accompanied by any deterioration in symptoms or exercise capacity. The lack of clinical deterioration after the withdrawal of digitalis was confirmed in another double-blind, placebo-controlled trial by Gheorghiade et al. (3), who noted no significant changes in symptoms, left ventricular ejection fraction or exercise duration in patients with chronic heart failure in whom digitalis was withdrawn for 1 month. In a third, recently completed, double-blind crossover study of digoxin in patients with chronic heart failure due to ischemic heart disease, Fleg et al. (4) found that digitalis produced a significant increase in systolic blood pressure and left ventricular ejection fraction at peak exercise, but these hemo-